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**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Application Number: 10/716,982
Filing Date: November 19, 2003
Appellant(s): LIPPS ET AL.

John R. Casperson
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed October 17, 2008 appealing from the Office action mailed April 14, 2008.

The appeal brief is filed in the new format under the revised BPAI final rule before the effective date of the BPAI final rule. The Office published the BPAI final rule to amend the rules governing practice before the BPAI in *ex parte* patent appeals. *See Rules of Practice Before the Board of Patent Appeals and Interferences in Ex Parte Appeals; Final Rule, 73 FR 32938 (June 10, 2008), 1332 Off. Gaz. Pat. Office 47 (July 1, 2008).* However, the effective date for the BPAI final rule has been delayed. *See Rules of Practice Before the Board of Patent Appeals and Interferences in Ex Parte Appeals; Delay of Effective and Applicability Dates, 73 FR 74972 (December 10, 2008).* In the notice published on November 20, 2008, the Office indicated that the Office will not hold an appeal brief as non-compliant solely for following the new format even though it is filed before the effective date. *See Clarification of the Effective Date Provision in the Final Rule for Ex Parte Appeals, 73 FR 70282 (November 20, 2008).* Since the appeal brief is otherwise acceptable, the Office has accepted the appeal brief filed by appellant.

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**(4) Status of Amendments After Final**

The appellant's statement of the status of amendments after final rejection contained in the brief is incorrect in that the entered amendment after final is dated June 23, 2008 not June 21, 2008.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

**WITHDRAWN REJECTIONS**

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner. The rejection of claim 24 under 35 U.S.C. 112, second paragraph set forth in sections 3-5, page 2, of the Final Rejection of April 14, 2008 .

**(7) Claims Appendix**

The statement of the status of claims contained in the brief is correct.

**(8) Evidence Relied Upon**

1. Boyd (The Basic Science of Oncology, 1992, McGraw-Hill, Inc., p. 379).

2. Stites et al (Medical Immunology, 9th Ed, Appleton and Lange, 1997, page 250-251).

3. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p. 4).

4. Dermer (Bio/Technology, 1994, 12: 320).

5. Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25).

6. Zellner et al (Clin. Can. Res., 1998, 4:1797-1802).

7. Embleton et al (Immunol Ser, 1984, 23:181-207).

8. Clark et al. (US Pat. App. Pub. 2006/0019256, January 2006).

**(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

***Claim Rejections - 35 USC § 112***

A. The rejection of claims 1-3, 8-12, 16, 17, 20 and 24 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained for the reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4)

the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a non-invasive cancer screening method comprising a) providing a mixture of proteonic cancer markers from different types of cancer cells, said mixture containing proteonic cancer markers identified and markers not yet identified; b) forming polyclonal antibodies against the mixture; c) forming a reagent from said polyclonal antibodies; d) obtaining a saliva sample from a human not diagnosed with cancer; e) bringing said saliva sample together with the reagent to form an assay sample, and f) assaying the sample by simple ELISA to determine whether an immunological reaction has occurred in the assay sample. wherein ELISA test results higher than a predetermined value are indicative of a positive screening test for cancer OR a non-invasive cancer screening method comprising a) providing a mixture of proteonic cancer obtained from breast, liver, colon, and ovarian cancers, said mixture containing proteomic cancer markers identified and markers not yet identified; b) forming polyclonal antibodies against the mixture; c) forming a reagent from said polyclonal antibodies; d) obtaining a saliva sample from a human not diagnosed with cancer; e) forming a saliva sample from the specimen f) bringing said saliva sample together with the reagent to form an assay sample, and g) assaying the sample by simple ELISA titer test to determine whether an immunological reaction has occurred in the assay sample, wherein ELISA test results of greater than 1:1000 are indicative of a positive screening tests.

The specification teaches that lysates from four cells lines, HT-29/breast cancer, Diji/colon cancer, CCL-13/liver cancer , and Sk-ov-3/ ovarian cancer or a mixture of lysates, denoted proteonic cancer markers (PCM), from all four cell lines was used to make polyclonal

antibodies, see p. 7-8. The specification teaches that the proteonic cancer markers were immunogenic, see p. 9 and Table 1. The specification teaches that using the polyclonal antibodies to the mixture of cell lysates from the four cancer cells most saliva specimens from normal individuals had a titer less than 1000, see p 9 and 10 and table 2. The specification teaches that titers above 1:1000 were tentatively considered positive for early diagnosis of cancer, see p. 10, lines 12-13. The specification teaches that saliva samples from normal individuals with titers greater than 1:1000 were also reactive with polyclonal antibodies produced to the individual cancers, see p. 11 and table 3. The specification teaches that polyclonal antibodies against the mixture of cancer lysates produced titers of 1800 to 3600 when saliva samples from stomach, lung and breast cancer patients were used and a titer of 450 in saliva samples from a post-treatment prostate/vocal cancer patient, see p. 12 and Table 4. The specification teaches that the PCMs in the prostate/vocal cancer patient should have been higher and suggests that treatment brought the level of PCMs down.

One cannot extrapolate the teachings of the specification to the enablement of the claims because the specification gives insufficient guidance and direction as to what predetermined value in the ELISA test is indicative of a positive screening test for cancer. The specification appears to arbitrarily choose a titer of 1:1000 as a cutoff for a positive test, see p. 10. The specification then tests saliva samples from normal individuals with a titer greater than 1:1000 against the individual PCM antibodies and finds reactivity with the individual PCM polyclonal antibodies, see p. 11 and Table 3. However, there is no evidence presented that these individuals with the titers greater than 1000 actually have cancer and, thus, these high titers could be present in the absence of cancer. Additionally, in the prostate/vocal cancer patient with the low PCM

titer it is unclear as to when the sample was taken and whether the patient was cancer free at the time and, thus, this low titer could be occurring in the presence of cancer. Thus, the only predetermined value taught in the specification a titer of 1:1000 is not predictably useful for indicating a positive test for cancer as the claimed method gives values above 1:1000 in individuals that are apparently normal and also produces values below 1:1000 in individuals who appear to have cancer. Given that Boyd (The Basic Science of Oncology, 1992, McGraw-Hill, Inc., p.379) teaches that diagnostic tests are used to distinguish patients with and without a particular disease, see p.379, right column, one of skill in the art could not predictably use the claimed method without undue experimentation as the only predetermined value taught in the specification as indicative of cancer does not predictably indicate a positive screening test for cancer.

Furthermore, Stites et al (Medical Immunology, 9th Ed, Appleton and Lange, 1997, page 250-251) teaches the importance of cut-off points in diagnostic tests. Although the claims are drawn to screening, given that the positive screening test is determined by an ELISA test higher than a predetermined value, the teachings of Stites are relevant to the claimed methods. Stites et al specifically teaches that when any diagnostic test is used to make a decision, there is some probability of drawing an erroneous conclusion and that predictive value theory can be used to deal with this problem. The reference further teaches that diagnostic sensitivity is defined as the fraction of diseased subjects with abnormal test results and that diagnostic specificity is defined as the fraction of nondiseased subjects who have a normal laboratory test. Further, Stites et al teach that the positive predictive value is the fraction of abnormal tests that represent disease and the negative predictive value is the fraction of normal tests that represent the absence of disease

(p. 251, col. 1). Stites et al specifically teach that diagnostic sensitivity and specificity reveal something about the test *given prior knowledge about the disease status* (emphasis in the original document), whereas positive and negative predictive values *estimate the likelihood of disease given the test result* (emphasis in the original document). Clearly it is the latter case that is of interest when trying to make a diagnosis (p. 251, col. 2). The difficulty with the determination of the positive predictive value for the claimed method, is that neither the claims nor the specification provide sufficient guidance on how to determine the positive predictive value for a positive screening test for cancer. Given that the only predetermined value taught in the specification (a titer of 1:1000) and claimed as indicative of cancer does not predictably indicate a positive screening test for cancer, as it cannot be determined from the teachings of the specification if individuals with titers above 1000 are positive for cancer or if individuals below 1000 are negative for cancer. Thus one of ordinary skill in the art could not predictably use the method as claimed without undue experimentation in the absence of further guidance and direction.

Additionally, even if an appropriate cutoff value were to be identified, one of skill in the art would not predictably expect that the broadly claimed mixture of cancer cells methods would work using all cancer cells, which is inclusive of cancer cell lines, which do not predictably express the same protein produced by tumors *in vivo* because of the artifactual nature of cultured cells.

In particular the characteristics of cultured cell lines generally differ significantly from the characteristics of the primary tumor. As discussed in Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p. 4), it is recognized in the art

that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, a petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer further teaches that when a normal or malignant cell adapts to immortal life in culture, it takes an evolutionary-type step that enables the new line to thrive in its artificial environment and thus transforms a cell from one that is stable and differentiated to one that is not. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Further, the art recognizes the problem of molecular artifacts associated with cell culture. For example, Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded. This is exemplified by the teachings of Zellner et al (Clin. Can. Res., 1998, 4:1797-1802) who specifically teach that products are overexpressed in glioblastoma

(GBM)-derived cell lines which are not overexpressed *in vivo*. Drexler et al further teach that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactual antigens can occur as a result of culture (see attached abstract). Additionally Clark et al. (US Pat. App. Pub. 2006/0019256, January 2006) teach that "[a]lthough cell lines have led to remarkable advances in our understanding of the molecular and biochemical changes in cancer cells, their use in the identification of effective cancer therapies is somewhat limited. Cell lines are imperfect predictors of drug efficacy in de novo tumors. Several factors likely account for this deficiency. Cancer cell lines are selected from a sub-population of cancer cells that are specifically adapted to growth in tissue culture and the biological and functional properties of these cell lines can change dramatically. Furthermore, cancer cells from only a minority of breast cancer tumors establish cell lines or xenograft tumors. The phenotypic and functional characteristics of these cell lines can change drastically relative to their properties in vivo. For example, the marker expression of both normal hematopoietic and leukemic tissue culture cells can change rapidly in tissue culture and often does not reflect that of the original stem cells from which they were derived . . . Taken together, these observations suggest that the biological properties of cell lines can differ markedly from the cancer cells from

which they were derived. This likely explains at least in part why the cell lines often are poor predictors of a drug's efficacy in the clinic," see para. 0109.

Given that cultured cell lines do not predictably express the markers expressed by tumor cells *in vivo*, one of skill in the art would not predictably expect that all mixtures of proteonic cancer markers identified and not yet identified from different types of cancer cells would be useful for the generation of polyclonal antibodies to form a reagent for cancer screening using saliva samples from patients. Given the above, one of skill in the art would not believe it more likely than not that the claimed invention would function as claimed for the screening of cancer without undue experimentation.

The specification provides insufficient guidance with regard to these issues and provides insufficient working examples which would provide guidance to one skilled in the art and insufficient evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

B. The rejection of claims 1-3, 8-12, 16, 17, 20 and 24 as failing to comply with the written description requirement is maintained for the reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to using a mixture from different types of cancer cells containing proteonic cancer markers identified and markers not yet identified or a mixture of proteonic cancer obtained from breast, liver, colon, and ovarian cancers, said mixture containing proteomic cancer markers identified and markers not yet identified. The claims lack any limitation on said mixtures containing proteonic cancer markers identified and markers not yet identified. When given the broadest reasonable interpretation, the terms "a mixture from different types of cancer cells containing proteonic cancer markers identified and markers not yet identified or a mixture of proteonic cancer obtained from breast, liver, colon, and ovarian cancers, said mixture containing proteomic cancer markers identified and markers not yet identified" encompasses numerous combinations of numerous types of cancer cells containing multiple cellular component such as a protein, nucleic acid, lipids, ions, other small intracellular molecules, a carbohydrate or polysaccharide, thus the genus of mixtures is highly variant which vary significantly both in structure and function from each other. The description of a mixture of markers from the HT-29/breast cancer, Diji/colon cancer, CCL-13/liver, and Sk-ov-3/ovarian cancer cells fails to adequately describe the genus of mixtures because said genus tolerates members which differ significantly in both structure and function from the mixture of markers from the HT-29/breast cancer, Diji/colon cancer, CCL-13/liver, and Sk-ov-3/ovarian cancer cells. One of skill in the art can reasonably conclude that applicant was not in possession of a genus of "a mixture from different types of cancer cells containing proteonic cancer markers identified and markers not yet identified" at the time the invention was filed. Because the genus of a mixture from different types of cancer cells containing proteonic cancer markers identified

and markers not yet identified is not adequately described, the method claims relaying on said genus are also not adequately described.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

In the instant case the genus is only described as a definition by function (i.e. the ability to form polyclonal antibodies), and beyond that example of a mixture of markers from the HT-29/breast cancer, Diji/colon cancer, CCL-13/liver, and Sk-ov-3/ ovarian cancer cells, one of skill in the art cannot readily visualize or recognize the identity of members of the genus.

**(10) Response to Argument**

A. Lack of enablement

Appellant argues that it is stated on page 5 of the Final Rejection, first full paragraph, that "One cannot extrapolate the teaching of the specification to the enablement of the claims because the specification gives insufficient guidance and direction as to what predetermined value in the ELISA test is indicative of a positive screening test for cancer .... the only predetermined value taught in the specification a titer of 1:1000 is not predictably useful for indicating a positive test for cancer as the claimed method gives values above 1:1000 in individuals that are apparently normal and also produces values below 1:1000 in individuals who appear to have cancer..."

Appellant argues that they first responded to this point in the amendment filed June 21, 2008, pages 8-10. MPEP 2164 discusses the enablement requirement. The factors to be considered are (A) The breadth of the claims (B) The nature of the invention (C) The state of the prior art (D) The level of one of ordinary skill (E) The level of predictability in the art (F) The amount of direction provided by the inventor ((3) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Appellant argues that each of the claims is directed toward "A non-invasive cancer screening method". Appellant argues that the difference between a screening method and a diagnostic method is that a screening method assigns nonsymptomatic patients to a risk category, whereas a diagnostic method determines whether or not a patient has a disease. Appellant argues that the arguments set forth in section 6 of the Final Rejection relate largely to diagnostic methods, which is not the nature of the invention. When the claimed screening method is carried out, a patient that has a test result over a predetermined value (for example, 1000) is at higher risk for cancer than a patient that has a test result of less than a predetermined value (for example, less than 1000). Appellant argues that as is well known to those skilled in the art, (persons possessing doctorate degrees and several years of experience) the predetermined value can be moved higher to reduce the number of false positive test results, or lower to reduce the number of false negative test results. Appellant argues that there is no magic number, and the failure of the specification to provide one does not establish a meritorious case of nonenablement. Appellant argues that based on the description and examples, and the skill level of the art, a suitable predetermined value for the screening test cutoff can be determined without unreasonable experimentation (Claims l-3, 8-10, 11-12 and 20-24), and need not be determined at all for claims 16-17, which state that it is to be 1:1,000.

Appellant's arguments have been considered, but have not been found persuasive. Although the claims are not specifically drawn to a diagnostic test, even a screening test must have a cutoff point for a positive or negative result for the screening test to be useful thus the references on diagnostic tests and cut-off points are pertinent to the instant rejection. The specification appears to arbitrarily choose an antibody titer of 1: 1000 for markers in the saliva as

a cutoff for a positive test, see p. 10. In 32 samples from normal individuals, 8 people have antibody titers above 1000, with some well above 1000, see Tables 2 and 3. Thus, 25% of the normal individuals would have a false positive test with the titer contemplated and specifically claimed as a cutoff in claim 16. Additionally, some of the normal individuals show titers that overlap and/or exceed the titers observed with saliva samples from cancer patients see Table 3 (normal) and Table 4 (cancer). Furthermore, no evidence has been presented that individuals with the high titers in Table 3 have any form of cancer. Thus, with a false positive rate of at least 25% and normal individuals showing titers equal to or in excess of those observed in cancer patients, one of skill in the art would not be able to predictably use the claimed methods for cancer screening without undue experimentation.

Appellant argues that on page 2 of the advisory action dated September 4, 2008, the examiner states "Although the method is drawn to screening and one of skill in the art could adjust the cutoff point to reduce the number of false positive test results, or lower it to reduce the number of false negative test results, given that the ELISA titers for the proteonic polyclonal antibodies exhibit significant over lap between samples from what appears to be normal individuals, Tables 2 and 3, and cancer patients, Table 4, with titers over 1:1000 in both groups, one of skill in the art would not predictably be able to use the claim methods for cancer screening for the reasons previously set forth."

Appellant argues that Table 3 is a subset of Table 2. Of the individuals from the general population tested in Table 2, approximately 1/4 had an ELISA titer from the mixed antibodies of the broad claims (PCM mix) of greater than 1:1000, and these patients are further the subjects in Table 3. Appellant argues that of the cancer patients tested in Table 4, 4/5 had an ELISA titer

from the mixed antibodies of the broad claims (PCM mix) of greater than 1:1000, the exception being a prostate/vocal cord cancer victim who had undergone treatment. (Specification, pages 9-11). Appellant argues that a cursory inspection of the Table 4 data reveals that, with the exception of the prostate/vocal cord cancer victim, the lowest cancer-victim ELISA titer against PCM mix is 1800, and in Table 2, the highest screening-test ELISA titer against PCM mix is 1600, so the examiner's contention that there is significant overlap is misleading. Appellant argues that selecting an ELISA titer of 1700, for example, would provide a clearer numerical demarcation, albeit with the concomitant certainty of a higher number of false negatives. The appellants selected a cutoff of 1,000 in their experimental. The examiner has not shown that the cutoff fails to divide the population into lower and higher risk portions or that one of skill in the art would not predictably be able to use the claim methods even without a specific numerical limitation for cancer screening.

Appellant's arguments have been considered, but have not been found persuasive. As set forth above with a false positive rate of at least 25% and normal individuals showing titers equal to or in excess of those observed in cancer patients, one of skill in the art would not be able to predictably use the claimed methods for cancer screening without undue experimentation. Appellant's argument with regard to the PCM mix markers not showing overlapping titers in cancer and normal saliva is not found persuasive because the claims are not limited to using the PCM mix or using a cutoff of 1700, in fact claim 16 specifically claims ELIA titer test results greater than 1:1000 as indicative of a positive screening test for cancer and 8 of the 32 normal individuals exhibit a titer above 1000 using the various marker antibodies examined, see Tables 2 and 3. Thus, one of skill in the art would not predictably use the claimed method for cancer

screening in the absence of further guidance or direction as to what test results would predictably be indicative of cancer.

Appellant argues that it was argued in the final rejection dated April 14, 2008, pages 7-10, that the specification is not enabling for using the range of proteonic cancer markers within the scope of the claims, specifically those derived from in vivo sources. Appellant responded in the responsive amendment filed June 21, 2008, as follows:

Appellant argues that the examples in the specification show the recovery of proteonic cancer markers used in the making of antibodies from in vitro sources. Appellant argues that the claims would include proteonic cancer markers from in vivo sources. Proteonic cancer markers from in vivo sources would be expected to produce more efficacious antibodies for carrying out the invention than those from in vitro sources, since "real life" antigens would produce antibodies which effective against them. The situation is non-analogous to (non-antibody-based) cancer drug efficacy, where in vitro efficacy is not a good predictor of in vivo efficacy. The invention is not an anti-cancer drug. Additionally, appellant argues that the invention has been demonstrated in a living system, and this is shown in the examples. Because the specification shows antibody operability from PCMs derived from in vitro sources, antibody operability for PCMs derived from in vivo sources is fairly established. It is additionally pointed out presently that claims 16- 17 are limited to "providing a mixture of proteonic cancer markers obtained from breast, liver, colon, and ovarian cancers" which is closely supported by the experimental data of the application.

Appellant argues that the examiner responded on page 2 of the advisory action dated September 4, 2008 as follows:

> "Although antibodies produced proteonic cancer markers from in vivo sources could potentially be used as claimed, the claims are not so limited and, thus, this argument is not found persuasive. Given that the ELISA titers for the proteonic polyclonal antibodies produced from the in vitro cultured cell lines exhibit significant overlap between samples from what appears to be normal individuals, Tables 2 and 3, and cancer patients, Table 4, with titers over 1:1000 in both groups, one of skill in the art would not predictably be able to use the claimed methods for cancer screening for the reasons previously set forth.

Appellant argues that the nature of the invention is cancer screening, as contrasted to cancer treatment. The chemical reactions occur in vitro, rather than in vivo, with the exception of polyclonal antibody production, and more predictable than in vivo reactions. The examiner advances no reason to doubt that proteonic cancer markers could not be obtained from in vivo produced cancers, or that those PCMs from in vivo sources would not result in the production of polyclonal antibodies, i.e., that those steps would be unpredictable. Appellant argues that in view of the nature of the invention, the relative predictability of the chemistry involved, and the skill of the art, it is submitted that claims are enabled and the examiner's rejection is in error and should be reversed.

Appellant's arguments have been considered, but have not been found persuasive. Although one of skill in the art could make antibodies from in vitro or in vivo sources of cancer cells, this does not mean that the antibodies so generated will bind to cancer markers. The majority of proteins in cancer cells are not distinct in structure or expression from those found in normal cells and thus would not be useful for distinguishing between normal and cancer. Additionally, cancers are heterogeneous in their phenotypes with respect to each other and

markers for one cancer would not predictably be expected to be a marker for another cancer, Furthermore, to be useful in the claimed method the proteonic markers would need to be found in the saliva. Thus one of skill in the art could not predictably make and use said mixture of cancer markers because the specification has as not specifically identified a combination of proteonic cancer markers identified and not yet identified, but the claims require providing a mixture of markers from cancers that are identified and not yet identified and the sources of these markers include cell lines as contemplated in the specification and specifically claimed in claim 24. As set forth in the Office Action of April 14, 2008 cell lines are well known in the art to exhibit phenotypes and antigen expression patterns that are distinct from those observed in primary tumors as a result of continuous culture of the cells and the artificial environment in which they are maintained. Thus one of skill in the art could not predictably make and use a mixture of proteonic markers that are identified and not yet identified as claimed given that the specification has not specifically identified such a combination markers and the source of such markers include cell lines which would not predictably be expected to be useful for obtaining markers as they are not representative of cancer cells in the *in vivo* situation as the phenotypes of cells *in vitro* and the antigens they express differ from cells in the in the *in vivo* situation as previously set forth.

B. Written Description

Appellant argues that on page 11 of the final rejection, it is stated "Because the genus of a mixture from different types of cancer cells containing proteonic cancer markers identified and markers not yet identified is not adequately described, the method claims relaying on said genus are also not adequately described."

Appellant argues that on page 12 of the Final Rejection, it is stated "the genus is only described as a definition by function (i.e. the ability to form polyclonal antibodies), and beyond that example of a mixture of markers from the HT-29/breast cancer, Diji/colon cancer, CCL-13/liver, and Sk-ov- 3/ovarian cancer cells, one of skill in the art cannot readily visualize or recognize the identity of members of the genus."

Appellant argues that it is stated on page 11 of the final rejection that

"One of skill in the art can reasonably conclude that applicant was not in possession of a genus of a mixture from different types of cancer cells containing proteonic cancer markers identified and markers not yet identified" at the time the invention was filed."

Appellant argues that the recitation of the "genus" in the claims must be evaluated in view of the prior art and the level of skill in the art in order to determine whether it is adequately disclosed. Claim 1 recites: "providing a mixture of proteonic cancer markers from different types of cancer cells, said mixture containing proteonic cancer markers identified and markers not yet identified". Different types of cancer cells were known to the art. It was known that cancer cells produced proteonic cancer markers, some of which were known and others not. What was not known was putting these proteonic cancer markers in a mixture. The level of skill in the art is mostly likely a doctorate degree and several years of research experience. Making a mixture of known materials is well within the level of skill. Furthermore, the specification provides a description of 4 "species" within the "genus" and demonstrates operability for them, and these are set forth in claim 16 as "a mixture of proteonic cancer markers obtained from breast, liver, colon, and ovarian cancers, said mixture containing proteonic cancer markers identified and

markers not yet identified" so at least claim 16 should be in compliance. Appellant argues that the specification furthermore mentions at page 5, lines 9-14 that the

> "cell line can be selected from the group consisting of a breast cancer cell line, a lung cancer cell line, a stomach cancer cell line, a liver cancer cell line, a colon cancer cell line, an ovarian cancer cell line, a cervical cancer cell line, a mouth/pharynx cancer cell line, a skin cancer cell line, a pancreatic cancer cell line, a testes cancer cell line, a brain tumor cell line, and a prostate cancer cell line."

Appellant argues that because of these factors, and because of the disclosure of representative species over the scope of the claims, it is submitted that all claims are in compliance with the written description requirement.

Appellant's arguments have been considered, but haven not been found persuasive. Although one of skill in the art could make cell extracts that have a mixture of proteins and other cellular constituents that may or may not be cancer markers, the claims are drawn to providing a mixture of proteonic cancer markers from different cancer cells or cancers said, mixtures containing proteonic cancer markers identified and markers not yet identified, not providing a cell extract. Thus, the claims require a description of said cancer markers identified and markers not yet identified. The specification has not described any combination of proteonic cancer marker and makers not yet identified, nor has it provided any relevant identifying characteristics of such markers. Appellant has only produced antibodies to cell extracts from cell lines to unknown antigens in the extracts, but have not described in any way what the antigens are. As set forth in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) the "naming a type of material generally known to exist, in the absence of knowledge

as to what that material consists of, is not a description of that material." In the instant case, the naming of cancer markers identified and markers not yet identified in cancer cells is not a description of the proteonic cancer markers.

Appellant argues that it is stated on page 2 of the advisory action dated September 4, 2008 that:

"...the proteonic markers for making the mixture are not known in art or taught by the specification. Although cancer cells were known in the art and one of skill in the art could make a mixture of lysates from those cells which would potentially contain the claimed known and unknown proteonic markers, the claims are not limited to mixtures of cancer cell lysates. Thus, given cancer cell, even specific cancer cell types, contain a myriad of potential known and unknown proteonic markers, none of which have been identified, one of skill in the art could not readily visualize the claimed genus, for the reasons previously set forth."

Appellant argues that the specification demonstrates in the examples that appellant had possession of an embodiment of the invention within the scope of the claims. Appellant argues that how to make the markers is taught. Appellant argues that how to use the markers to make the necessary antibodies is taught. Appellant argues that how to use the antibodies to conduct a screening test is taught. Appellant argues that no reason has been advanced to "doubt that appellant failed to do what is described in the examples, and the examples fairly support the constructive reduction to practice that is described in the specification. The specification as a whole would allow one of ordinary skill in the art to recognize that appellant invented what is claimed. Further, the level of skill and knowledge in the art is such that one would be able to follow the detailed steps of the claimed methods. Appellant argues that the practice of the

method requires no knowledge of the structures and properties of a compound that would predictably result in the desired activity; rather, the claimed invention is a screening method, not the compounds screened for or the compounds employed in the screening. Thus, one of ordinary skill in the art would conclude that appellant was in possession of the claimed method of screening for cancers at the time of filing.

Appellant's arguments have been considered, but have not been found persuasive. Appellant has not taught how to make the markers as appellant has not provided any relevant identifying characteristics, structural features, or functional characteristics with a known or disclosed correlation between the function and structure of the proteonic cancer markers identified and the markers not yet identified, nor is it clear how one could provide characteristics for makers that have not yet been identified. Without any knowledge of the structures or properties of the cancer markers identified or the markers not yet identified one of skill in the art cannot readily envision the genus claimed, particularly given that specification does not identify a single species of proteonic cancer marker not yet identified that can be used in the claimed method of screening for cancer.

Appellant argues that the Lilly case is not on point, as the unsupported (and un-described) "genus" there was a generically claimed, inadequately characterized, composition of matter which was asserted to be novel. The present claims are methods, and the materials employed are known and/or obtainable using the teaching of the specification and characterized functionally and by way of example.

Appellant's arguments have been considered, but haven not been found persuasive because Lilly is relevant to the instant case. Lilly states the "naming a type of material generally

known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." At 1568, 43 USPQ2d at 1406. In the instant case, the specification simply names cancer markers identified and markers not yet identified without any relevant identifying characteristics or description of their structure and the specification does not provide a single species of proteonic cancer marker not yet identified that can be used in the claimed method of screening for cancer. Thus the specification as filed fails to provide an adequate written description of a mixture of proteonic cancer markers identified and markers not yet identified from cancer cells or the specifically claimed cancers.

Appellant argues that in the advisory action dated September 4, 2008, it is stated:

> "...the proteonic markers for making the mixture are not known in the art or taught by the specification and thus, one of skill in the art could not readily visualize the claimed genus."

Appellant argues that it is not necessary to know what the markers are in order to practice the claimed method. Appellant argues that one must know how to obtain and use the markers, and this is taught by the specification.

Appellant's arguments have been considered, but have not been found persuasive because the initial step of the claimed method requires providing cancer markers identified and not yet identified and without a description of said markers one of skill in the art would not be able to provide such markers. Furthermore, although one could screen for cancer markers, screening assays are not sufficient to describe an invention because 35 USC 112 requires that the specification contains a written description so that one can make and use the invention, not screen for the invention. Furthermore, it is unclear how one of skill in the art would recognize

that he or she is in possession of a marker not yet identified as the marker is, by definition, not identified. Thus, for these reasons, the specification as filed fails to provide an adequate written description of a mixture of proteonic cancer markers identified and markers not yet identified from cancer cells or the specifically claimed cancers.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Peter J Reddig/

Examiner, Art Unit 1642

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/Larry R. Helms/

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